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Development of ionic and non-ionic natural gum-based bigels: Prospects for drug delivery application

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ABSTRACT: Recently, much attention has been focused on the development of gel based formulations for controlled drug delivery applications. Herein, we report the effect of the ionic (gum acacia) and the non-ionic (guar gum) gums on the properties of the bigels prepared with fluid-filled organogels. The microscopic study suggested the presence of flocculated structure in guar gum bigel, whereas, a de-flocculated structure was observed in gum acacia bigel. Infrared spectroscopy suggested the presence of polysaccharides in the bigels. The mechanical properties of the guar gum bigel were better than gum acacia bigel. The conductivity and the release properties suggested superior properties of gum acacia bigel. This indicated that the ionic nature of acacia bigel played a major role in controlled drug delivery, making it a potential bigel for desired pharmaceutical applications. © 2015 Wiley Periodicals, Inc. J. Appl. Polym. Sci. **2015**, *132*, 42561.

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INTRODUCTION

In the last 2 decades, there has been an increase in the development of biphasic formulations. This is due to the ability of the biphasic systems to accommodate both hydrophilic and hydrophobic drug molecules within the formulations.[1] The biphasic systems allow compartmentalization of the drugs in either of the phases, depending on the hydrophilic character of the drug molecules. The classical example of a biphasic formulations are emulsions. Emulsions are defined as liquid biphasic formulations. They are inherently thermodynamically unstable.[2] Although many attempts have been made to stabilize the polar–apolar interphase using emulsifiers, the stability of the emulsions still remains a concern. To eliminate this disadvantage, many researchers have proposed to modulate the viscosity of the external phase of the emulsions to such an extent that the dispersed phase becomes immobilized. These formulations are regarded as emulgels (emulsion gels).[3] The stability of the emulsions was improved to a great extent when converted to emulgels. But the leaching of the internal phase, on long-term storage, leads the scientists to look for more suitable formulations with better stability than the emulgels. Recently, some groups have proposed that the gelation of the internal phase might help in further improving the stability of the emulgels. The gellation of the internal phase will allow matching the viscosity of both the dispersed phase and the continuum phase thereby improving the compatibility of both the phases. These formulations have been named as bigels.[4–6]

Polysaccharides have found numerous applications in pharmaceutical industries for preparing gels and emulsions. This can be explained to the versatile properties of the polysaccharides. Commonly used polysaccharides in pharmaceutical industries include alginate, chitosan, pectin, guar gum, gum acacia, dextran, and xanthan gum.[7] Amongst the above-mentioned polysaccharides, guar gum and gum acacia have been studied since long for the preparation of gel based pharmaceutical formulations due to its binder, disintegrant, suspending, thickening, and stabilizing properties. Guar gum is obtained from the seeds of *Cyamopsis tetragonolobus*. It is a water-soluble non-ionic polysaccharide, which has been reported to be low cost, non-toxic, and biodegradable.[7,8] Gum acacia is a natural polysaccharide obtained from the plant *Acacia senegal*. It is also water-soluble in nature. Like guar gum, gum acacia is also cheap, non-toxic, and biodegradable. Additionally, gum acacia has been reported to have anti-bacterial and anti-inflammatory properties.[9]

Table I. Composition of the Bigels (for 10 g)

Formulations	S_{mix} (g)	Sunflower oil (g)	Guar gum (g)	Gum acacia (g)	Metronidazole (g)
G1	4.0	3.5	2.5	-	-
G1M	4.0	3.4	2.5	-	0.1
G2	4.0	3.5	-	2.5	-
G2M	4.0	3.4	-	2.5	0.1

In this study, we developed bigels using an anionic (gum acacia) and a neutral (guar gum) naturally occurring gums. The bigels were prepared using fluid-filled structure mechanism. The effect of the anionic and the neutral gums on the properties of the bigels was studied in-depth.

MATERIALS AND METHODS

Materials

Span 80, tween 80, and gum acacia were procured from Loba chemie, Mumbai, India. Guar gum was procured from HiMedia laboratories, Mumbai, India. Refined sunflower oil (Gold Winner®, Kaleesuwari Refinery Private Limited, Chennai, India) was procured from the local market. Double distilled water was used throughout the study.

Methods

Preparation of the Bigels. The bigels were prepared by fluid-filled structure mechanism as per our previously reported method with slight modifications.[10] The surfactant mixture of span 80: tween 80 (1 : 2, w/w) was used as the liquid gelator (S_{mix}). 4 g of the S_{mix} was dissolved in 3.5 g of the sunflower oil at room-temperature (25°C). To this solution of S_{mix} (50°C), 2.5 g of 1% (w/w) gum solution (gum acacia or guar gum) in water (50°C) was added drop-wise with continuous stirring at 1000 rpm to form a homogenous emulsion. Thereafter, the emulsion (50°C) was cooled down to room-temperature to induce gelation. The gelation of the formulations was confirmed by inverted-tube method (Table I). Drug (metronidazole was used as the model drug) containing formulations were prepared using drug containing liquid gelator (S_{mix}). Metronidazole (1% [w/w]) was first dissolved in liquid gelator (S_{mix}) and then the gelator was used for the preparation of bigels. Drug containing formulations were also prepared as mentioned above.

Microscopic Evaluation. The bigels were converted into thin smears and subsequently visualized under bright field microscope (Lieca DM 750 equipped with ICC50HD camera).[11]

FTIR Studies. The chemical interactions amongst the functional groups of the components of the bigels were analyzed using infrared (IR) spectroscopy. The analysis was performed in the ATR mode (ZnSe crystal) of the Alpha-E FTIR spectrometer, Bruker, Germany. The analysis was done in the wavenumber range of 500–4000 cm^{-1}.[12,13]

Mechanical Studies. The stress relaxation and the backward extrusion properties of the bigels were determined using a static mechanical tester (Stable Microsystems, TA-HDplus, U.K.). The crosshead speed of the probe was 1 mm/s during both the tests.[14]

Electrochemical Impedance Spectroscopy Studies. The electrical properties of the bigels were studied using a phase-sensitive multimeter (PSM1735, Numetriq, Japan). The bigels were filled in the cells. The internal diameter of the cells was 5 mm. The electrodes were placed 1 cm apart. An AC voltage of 100 mV was applied across the electrodes. The scanning was done in the frequency range of 0.1 Hz to 1.0 MHz.

Iontophoretic Drug Delivery. The release of metronidazole from the metronidazole (1%, w/w) loaded bigels was studied using an in-house developed iontophoretic drug delivery system. A sinusoidal constant current (32.13 μA, I_{rms}) was injected into the formulations using a stainless steel electrode (diameter: 1.4 cm). This resulted in the current density of 20.88 $\mu A/cm^2$. The donor contained 2.12 g of the drug loaded bigels. The receptor contained 25 mL of distilled water (37°C, 100 rpm) as the dissolution media. The donor was separated from the receptor using a pre-activated dialysis membrane (MW cut-off: 60 kDa, Himedia, Mumbai). About 3 mL of the dissolution media was sampled from the receptor at regular intervals (15 min) and was replaced with fresh distilled water. The sampled dissolution media were analyzed using a UV–vis spectrophotometer (UV 3200, Labindia, India) at 321 nm.[12]

RESULTS AND DISCUSSIONS

Preparation of the Bigels

The homogenized solution of S_{mix} in oil (sunflower oil) was transparent and pale brown in color. The addition of the gum solution to the S_{mix} solution resulted in the formation of white mixture, indicating the formation of an emulsion. The bigels appeared as milky-white due to the diffraction of the light from the interface of the polar and the apolar phases (Figure 1). The formulations formed were smooth to touch and gave a cooling sensation, when a thin smear was applied over the skin surface. There was no gritty feeling (often associated with the formulations made with solid gelator molecules) or odor. The prepared bigels were found to be hemocompatible in the presence of goat blood. The % hemolysis in the presence of the extracts of the bigels was <5%.

Microscopic Studies

The microscopic studies of the bigels showed the presence of spherical droplets within a matrix. Herein, the guar gum containing bigels showed the presence of agglomerated structures around the droplets (Figure 2). The formation of the agglomerated structures can be ascribed to the intermolecular interactions amongst the guar gum molecules. Earlier reports suggest that the water molecules usually surround these agglomerated structures of the guar gum in bigels.[15] Moreover,

Figure 1. Culture vials containing bigels: (a) G1 (guar gum bigel) and (b) G2 (gum acacia bigel). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

it is suggested that the function of water molecules is to stabilize the interface by forming an ordered layer around the interface of the oil molecules in a biphasic system.[16] A combination of the agglomeration of the guar gum and ordering of the water molecules may explain the formation of agglomerated structures around the apolar molecules. Conversely, acacia gum containing bigels did not show the formation of any agglomerated structures around the droplets, which can be explained by the anionic nature of the acacia gum that prevented the formation of agglomerates due to ionic repulsion. Because of this reason, the dispersed phase of the formulation was in de-flocculated state.

FTIR Studies

From the FTIR patterns of the bigel formulation, the broad peak observed at about 3400 cm^{-1} can be assigned to the presence of the extensive hydrogen bonding amongst the different components of these bigels. Herein, the relatively high intensity of this peak in the FTIR pattern of acacia gum containing bigel can be associated with the higher degree of hydrogen bonding. Whereas, the relatively less hydrogen bonding observed in the case of guar gum bigel can be understood from the greater level of hydrophobic interactions amongst the guar gum molecules, which in turn indicate towards the absence of those functional groups that can involve in hydrogen bonding. In addition to the peak at about 3400 cm^{-1}. The FTIR pattern also showed few other peaks in the range of 1500−1200 cm^{-1}, 1200−950 cm^{-1}, and 950−700 cm^{-1}. In view of previous reports, these peaks are most likely associated with the presence of polysaccharides.[17] In addition to these peaks, the dual peak observed in the range of 2900−2800 cm^{-1} can be associated with the fatty acid molecules of the sesame oil (Figure 3).

Mechanical Studies

While undertaking stress relaxation study, the maximum force (F_0) sensed by the probe while penetrating the bigels is considered as an indicative of the firmness of the gels.[14] Figure 4(a) shows that the F_0 of the guar gum bigel was much higher than the gum acacia bigel. This observation suggests that the interconnecting structure formed due to the hydrophobic interactions of the guar gum (as visualized from the microscopic studies) played an important role in improving the overall mechanical properties of the bigel. This can be also be accounted for the formation of a more ordered structure of the guar gum molecules around the apolar phase. Although, the hydrogen bonding was higher in the gum acacia bigel, the firmness was much lower. This may be due to the inability of the gum acacia to form a more ordered structure as compared to the guar gum, which caused a filler effect. While, the electrostatic repulsion of the polymeric chains due to the stearic effect of the carboxylic groups could also be another possible cause of this low firmness. The relaxation profile was analyzed using modified Peleg's equation [Figure 4(b,c)]. The results from this analysis reveal that the initial rate of relaxation (k_1) was higher

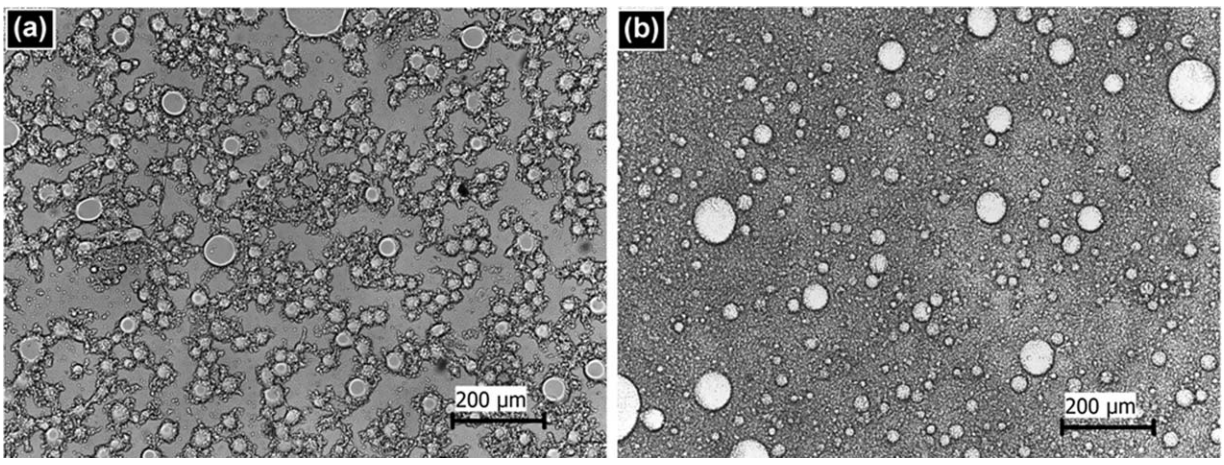

Figure 2. Bright field micrographs of: (a) G1 (guar gum bigel) and (b) G2 (gum acacia bigel).

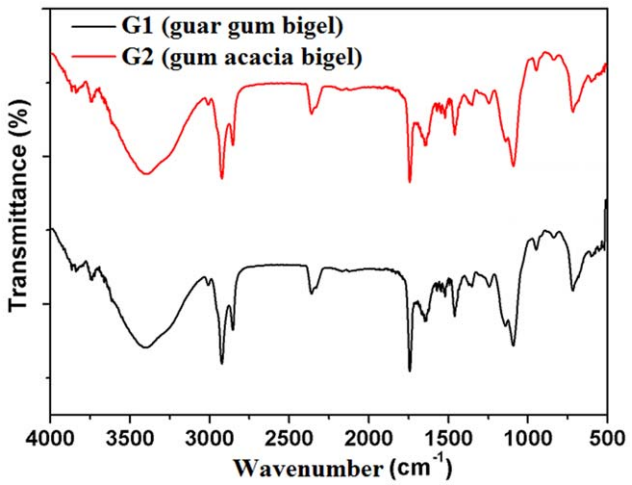

Figure 3. FTIR spectra of bigels. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

in the guar gum bigel as compared to gum acacia bigel but the extent of relaxation (k_2) was similar in both bigels. Hence, it is suggested that although the firmness of the guar gum bigel is higher, the microarchitecture of the bigel is flexible enough to quickly reorient its microarchitecture, so as to relieve the applied stress. The area under the normalized stress relaxation curve (S^*) is closer to 1 for the elastic materials, while it is closer to 0 for the viscous fluids. Literature suggests that the "S^*" values in between 0 and 1 are indicative of the viscoelastic materials.[18] The S^* values of both the bigels were found to be ~0.46 (Table II). This indicates a viscoelastic fluid-like nature of the prepared bigels.

The observed non-linear viscoelastic nature of the bigels was further investigated and described using Wiechert model. This mathematical model describes the viscoelastic behavior in a more precise way using a combination of spring and dashpot elements.[19] In this study, three Maxwell elements were used to fit the stress relaxation data of the bigels [insert, Figure 4(e)].[20] Here, the Wiechert model is expressed as follows;[20]

$$P_{(t)} = P_0 + P_1.e^{-t/\tau_1} + P_2.e^{-t/\tau_2} + P_3.e^{-t/\tau_3}. \quad (1)$$

In eq. (1), $P(t)$ is the magnitude of the decaying force at time t; P_0 is the magnitude of the residual force; P_1, P_2, and P_3 are the relaxation modulus of the spring, while τ_1, τ_2, and τ_3 are the relaxation time of the dashpot during the stress relaxation test. Least-square difference regression method was used to fit the stress relaxation data using solver add-in option in Microsoft excel 2007. The coefficient of viscosity of the dashpots (η_1, η_2, and η_3) was calculated by multiplying the relaxation time of the dashpot (τ_1, τ_2, and τ_3) to elastic modulus values of the spring (P_1, P_2, and P_3) (Table III).[21]

As can be seen in Table III, the P_0 value was higher in G2 as compared to G1. In contrast, the P_1 and P_2 values were lower in G2 compared to G1. Interestingly, the P_3 values for both bigels were nearly the same. Table III also shows that the relaxation time of the dashpots during the stress relaxation test (τ_1, τ_2, and τ_3) was significantly higher in G1 compared to G2. This observation indicates towards the restricted movement of the polymer molecules in G1 compared to G2. This observation is concurrent with the prior mentioned observation of higher firmness of G1 as compared to G2 (as observed from the F_0 values). Finally, the coefficients of viscosity (η_1, η_2, and η_3) of the dashpots were found higher in G1 as compared to G2.

The index of viscosity of the bigels was determined by backward extrusion method. The method deals with the determination of the work done to move out of the formulations, after being completely submerged. The backward extrusion test showed much higher index of viscosity in guar gum bigel as compared to gum acacia bigel [Figure 4(f)]. The results were concurrent with the coefficient of viscosity (η_1, η_2, and η_3) calculated from the Wiechert mechanical modeling of the stress relaxation studies. The results may be explained by the ordered structure of the guar gum bigel and predominant electrostatic repulsion amongst the polysaccharide molecules in the gum acacia bigel.

Electrochemical Impedance Spectroscopy Studies

The electrochemical impedance spectroscopy (EIS) is a very important tool, which can assist in differentiating the materials in terms of their conductive behavior. Herein, we performed the conductivity analysis of the two bigels using EIS technique. Interestingly, the Nyquist plots obtained from the EIS analysis of the two bigels were almost same in shape with a perfect semi-circle observed for both gel samples. It can be seen that the guar gum-based bigel (G1) showed the semi-circle profile with the touchdown point (on real axis) in the high frequency region, whereas the Nyquist plot for gum acacia based bigel (G2) showed a small semi-circle with touchdown point at significantly low frequency [Figure 5(a)]. This touchdown point at the real axis gives the values of bulk resistance (R_b) for both samples (G1 and G2). The results revealed that the G1 bigel displays high bulk resistance as compared to the G2 bigel, where the high bulk resistance in guar gum-based bigel (G1) can be associated with its uncharged nature compared to gum acacia based bigel (G2), which is intrinsically conductive due to its ionic nature. The electrical models of the bigels were predicted by fitting the impedance data of the Nyquist plot using Z SimpWin. To fit the data accurately, two constant phase elements (CPEs) were introduced to remove the inhomogeneity in these bigel samples. Here, the Constant Phase Element "CPE1" represents the electrical double layer formed at the sample–electrode interface and is responsible for the spike in the low frequency region. Conversely, CPE2 represents the bulk properties of the formulations.

The conductivity of the guar gum bigel was lower as compared to the gum acacia bigel [Figure 5(b)]. This was quite expected due to the higher bulk resistance of the guar gum bigel as compared to the gum acacia bigel (Table IV). The conductivity profiles of both bigels (G1 and G2) were nearly constant in the frequency range of 0 Hz and ~1200 KHz. Thereafter, there was an increase in the conductivities of the bigels as can be seen from [Figure 5(b)]. This was probably due to decrease in the polarization effect at the sample–electrode interface. The rate of increase in the conductivity was lower in the gum acacia bigel, which can be can be explained by the polyelectrolytic nature of

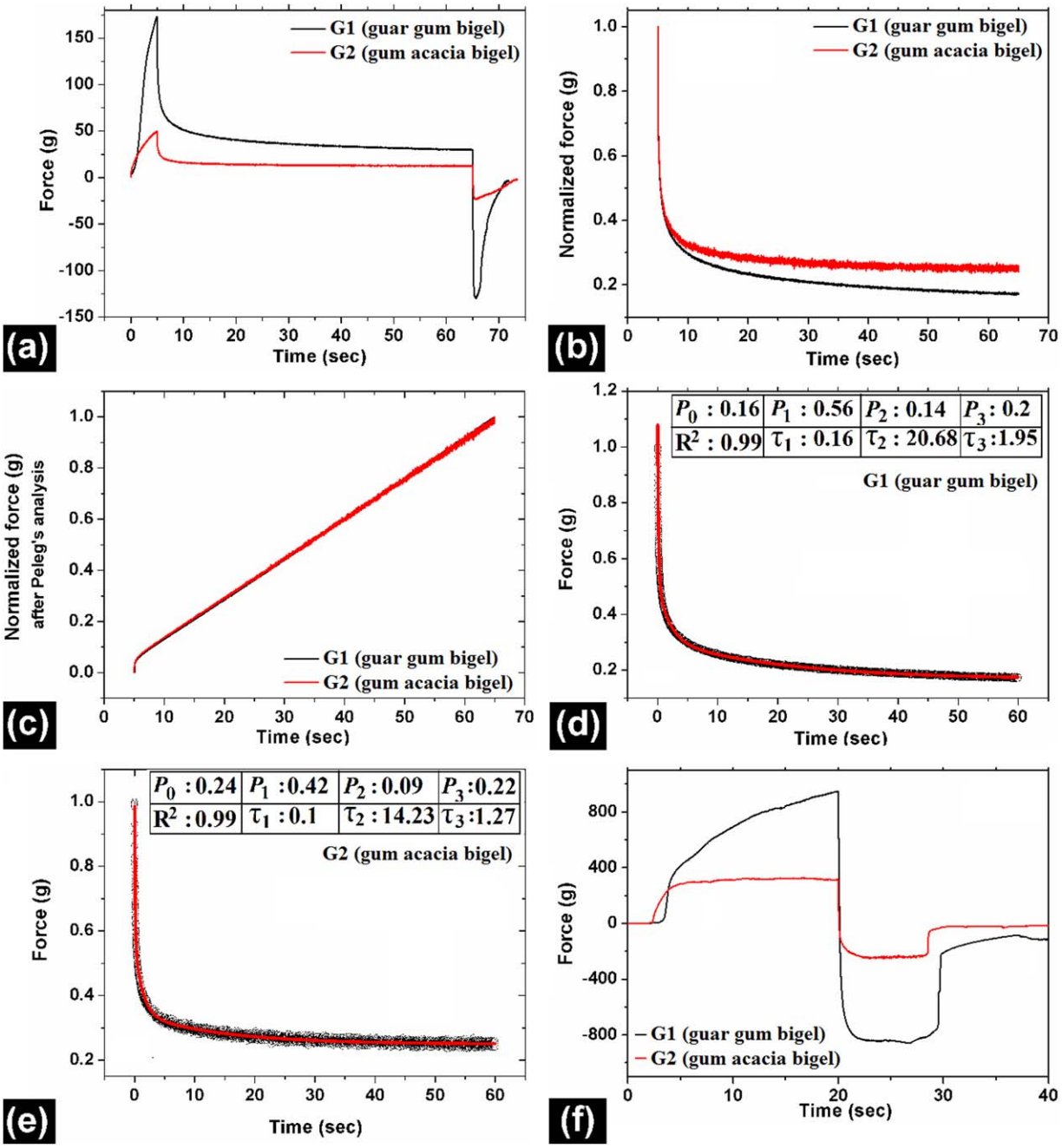

Figure 4. Mechanical properties of the bigels. Stress relaxation studies: (a) stress relaxation profile, (b) normalized force–time graph, (c) Peleg's analysis; Wiechert model fitting of: (d) G1 (guar gum bigel) and (e) G2 (gum acacia bigel); (f) Backward extrusion studies. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Table II. Stress Relaxation and Backward Extrusion Parameters

Formulations	F_0 (g)	F_r (g)	k_1	k_2	S^*	Firmness (g)	Consistency (g s)	Cohesiveness (−g)	Index of viscosity (−g s)
G1 (Guar gum bigel)	173.03	29.85	0.031	0.15	0.46158	829.068	11743.538	−839.949	−1909
G2 (Gum acacia bigel)	50.02	12.34	0.019	0.15	0.461586	301.877	5221.741	−180.198	−69

Table III. Wiechert Model Parameters for Stress Relaxation

Formulations	Stress relaxation model	Coefficient of viscosity of the dashpots
G1 (Guar gum bigel)	$P_{(t)}=0.16+0.56.e^{-t/0.16}+0.14.e^{-t/20.68}+0.2.e^{-t/1.95}$	$\eta_1=0.09$, $\eta_2=2.89$, $\eta_3=0.39$
G2 (Gum acacia bigel)	$P_{(t)}=0.24+0.42.e^{-t/0.1}+0.09.e^{-t/14.24}+0.22.e^{-t/1.27}$	$\eta_1=0.04$, $\eta_2=1.28$, $\eta_3=0.28$

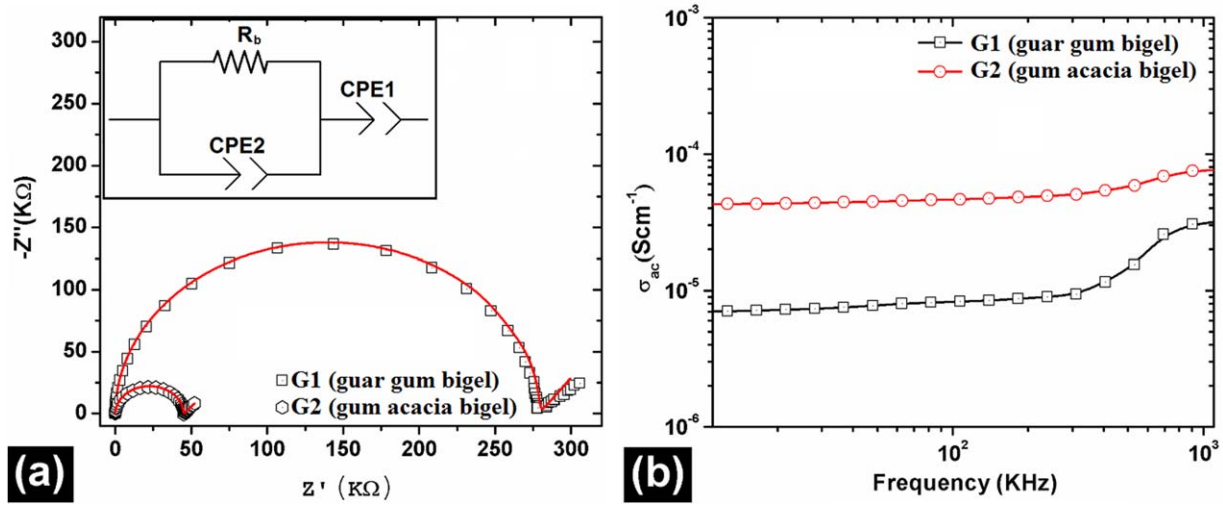

Figure 5. EIS profiles of the bigels (a) Nyquist plot (equivalent circuit diagram shown as insert) and (b) a.c. conductivity. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

gum acacia, which might help in minimizing the polarization effect.

Iontophoretic Drug Release Studies

To investigate the effect of the uncharged and charged nature of the two bigels (G1 and G2, respectively) on the drug delivery properties, herein, we performed the ionophoretic drug release studies of the two bigels. The results of the iontophoretic drug release studies are shown in Figure 6, which revealed that almost ~100% drug release was achieved upon using gum acacia bigel (G2M) within only 1.5 h. Conversely, it took almost 2 h to achieve ~85% of the drug release upon using guar gum bigel (G1M) as shown in Figure 6(a). The faster release of the drug from the formulations may be explained by the application of the electrical potential. In view of previous reports, the rate of drug release is higher from the formulations having higher conductivity. Hence, we suggest that the high rate of drug release found in the case of gum acacia bigel might be associated with its high conductivity.[22] An increase in the conductivity results in the diffusion of the solute molecules, which in turn, results in the increased drug release. Moreover, our observations from *in vitro* studies are also concurrent with this observed phenomenon.

Herein, we used the Weibull model to analyze the release pattern of the drug [Figure 6(b,c)]. The model is mathematically expressed as follows:[23]

$$m=1-\exp\left(\frac{-(t-T_i)^b}{a}\right). \quad (2)$$

In eq. (2), m indicates the amount of drug accumulated in the solution at time "t." "a" indicates the time scale parameter of the release process, "T" represents the lag time before the actual drug release starts and "b" indicates the shape of the release graph.

The data fitting was done using solver add-in of Microsoft Excel 2007 by non-linear least square difference method. Both the samples showed a good fit (accuracy >0.99). A "T" value of zero indicated no time lag for the release of the drug from the matrices. G2M showed higher "a" and "b" values compared to

Table IV. The Conductivity Analysis of the Bigels

Formulations	R_b (Ω) ($\times10^4$)	(S/cm) ($\times10^{-5}$)
G1 (Guar gum bigel)	27.90	0.70
G2 (Gum acacia bigel)	4.47	4.31

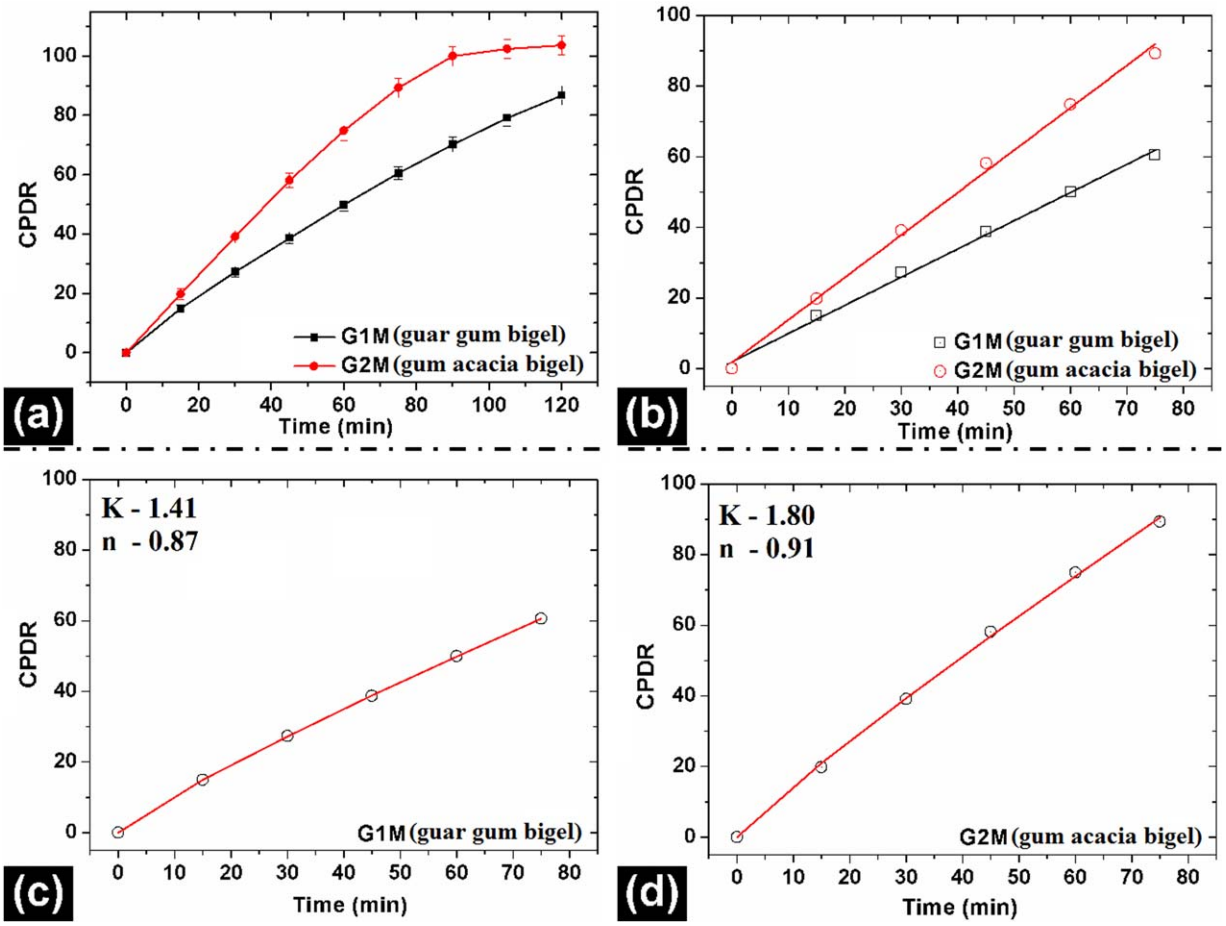

Figure 6. Drug release studies (a) CPDR; Weibull model fitting (b) G1M (guar gum bigel) and (c) G2M (gum acacia bigel); (d) zero order; KP model fitting (c) G1M (guar gum bigel) and (d) G2M (gum acacia bigel). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

G1M. The "*a*" value is an indicator of the time scale parameter. Higher "*a*" value is associated with the quick release of the drug. The results suggested that the release of the drug from G2M was higher than G1M. The "*b*" value is an indicator of the shape of the release profile. A "*b*" value >1 is an indicator of the S-shaped (sigmoidal) release profile. A higher "*b*" value for G2M suggested a more prominent sigmoidal release profile. This was also evident from the nature of the release profile curves.

Although Weibull model is useful in predicting the rate of release of the drug and the shape of the release profile, but it does not take into account of the interactions amongst the delivery matrix and the drug, in addition to the diffusion of the drug within the delivery matrix. Therefore, to develop an understanding of the mechanism of the release of the drug under the influence of the electric current, the release profiles were fitted to the different mathematical release models (zero-order, first-order, and Higuchi models) and Korsmeyer–Peppas (KP) diffusion kinetics model. The fitting of the results showed that the best-fit of the release data was zero-order model [Figure 6(d)]. Zero-order release behavior is often obtained from the formulations acting as a reservoir-type delivery vehicles. The release studies indicate that both the ionic and the non-ionic gum-based bigels behaved as the reservoir-type delivery vehicle under the influence of the electrical current. The release of the drugs from the reservoir-type delivery vehicle is usually diffusion-mediated. Here, the KP model [eq. (2)] was used to predict the mechanism of diffusion [Figure 6(e,f)]. The KP model is often defined as the power-law model as is expressed by the following relation;

$$\frac{M_t}{M_\infty} = k.t^n. \tag{3}$$

In eq. (3), M_t = amount of drug released at time "*t*"; M_∞ = amount of drug released at time "∞"; k = structural parameter of the formulations; n = diffusion exponent.

The KP model was also fit by non-linear least square difference method. The fitting of the model with the experimental data was display accuracy >0.999 in both the cases, indicating a good fit of the release behavior to the model. G1M and G2M bigels showed *n*-values of about ~0.87 and ~0.91, respectively [Figure 6(c,d)]. This suggested that the diffusion mechanism of the drug from both the formulations was anomalous; indicating the presence of more than one diffusion mechanisms prevalent during the release of the drug. The structural parameter (k) of G1M and G2M was 1.41 and 1.8, respectively. This indicated that the structure of the formulations was different from each

other. The results were concurrent with the microscopic studies and suggest that although both formulations were biphasic in nature, there was agglomeration of the polymeric phase around the apolar phase in guar gum bigel. No such agglomeration was observed in the case of gum acacia bigel.

CONCLUSION

In this study, non-ionic (guar gum) and ionic (gum acacia) gum-based bigels were prepared and characterized in view of their potential application for drug delivery. The study revealed that the microstructure of the guar gum bigel (G1) showed the presence of agglomerated structures across the dispersed globules, whereas, gum acacia based bigel (G2) did not show any such agglomerated structures around the dispersed globules. Based on the detailed analysis described above, we anticipate that the agglomerated structures in the G1 bigel had improved the droplet–droplet interactions, which might be responsible for the improved mechanical properties of this bigel. Conversely, the mechanical properties of the gum acacia bigel (G2) were found to be relatively poor compared to the guar gum bigel. Interestingly, although the mechanical properties of G1 bigel were better than G2 bigel, the conductivity analysis and drug release studies of the two bigels revealed that the gum acacia bigel (G2) was more potent than the guar gum bigel (G1). The observed result can be explained by the polyelectrolytic nature of the gum acacia, which might trigger the fast rate of drug release in this bigel.

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